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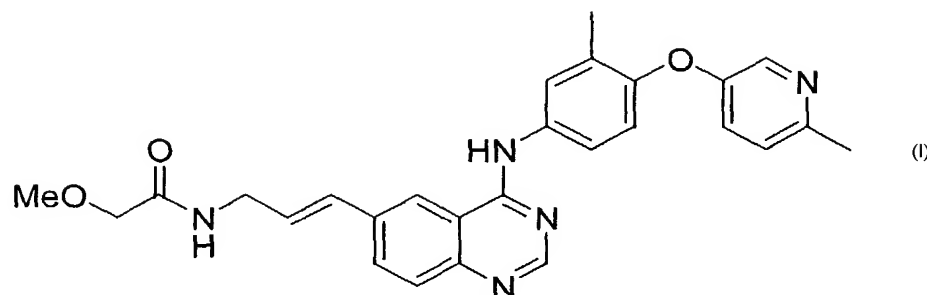
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(54) Title: SALT FORMS OF E-2-METHOXY-N-(3-(4-(3-METHYL-PYRIDIN-3-YLOXY)-PHENYLAMINO)-QUINAZOLIN-6-YL)-ALLYL)-ACETAMIDE, ITS PREPARATION AND ITS USE AGAINST CANCER



(57) Abstract: The invention relates to succinate and malonate salts of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide having formula (I). More particular the present invention relates to sesquisuccinate and di-malonate salts of formula (I). The invention also relates to pharmaceutical compositions containing the succinate and malonate salts of formula (I). The invention further relates to methods of treating hyperproliferative diseases, such as cancers, in mammals, especially humans by administering the above salts and to methods of preparing the above salts.

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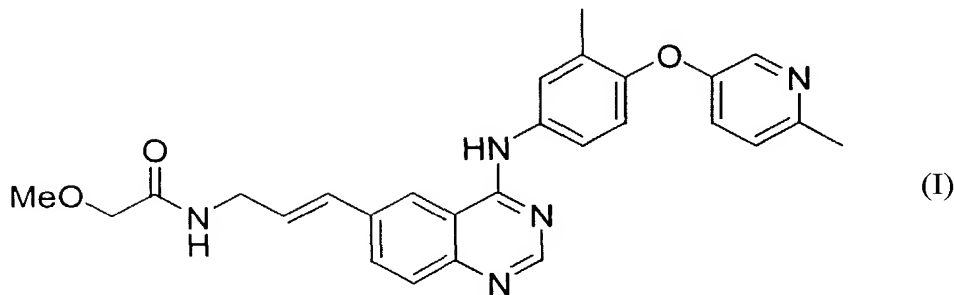
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(54) Title: SALT FORMS OF E-2-METHOXY-N-(3-{4-[3-METHYL-4-(6-METHYL-PYRIDIN-3-YLOXY)-PHENYLAMINO]-QUINAZOLIN-6-YL}-ALLYL)-ACETAMIDE AND METHOD OF PRODUCTION



(57) Abstract: The invention relates to succinate and malonate salts of E-2-Methoxy-N-(3-{4-[3- methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide having formula (I). More particular the present invention relates to sesquisuccinate and di-malonate salts of formula (I). The invention also relates to pharmaceutical compositions containing the succinate and malonate salts of formula (I). The invention further relates to methods of treating hyperproliferative diseases, such as cancers, in mammals, especially humans by administering the above salts and to methods of preparing the above salts.

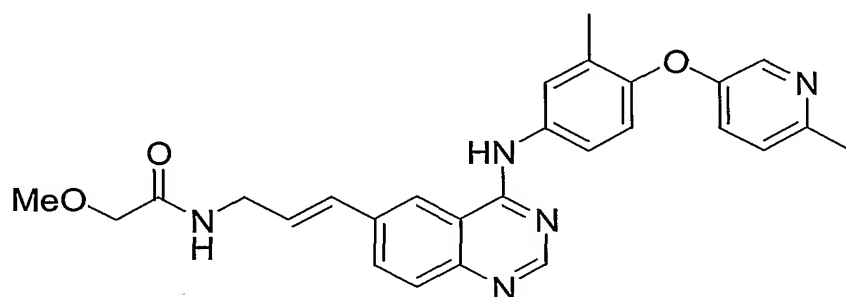


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SALT FORMS OF E-2-METHOXY-N-(3-{4-[3-METHYL-PYRIDIN-3-YLOXY}-PHENYLAMINO]-QUINAZOLIN-6-YL)-ALLYL)-ACET AMIDE, ITS PREPARATION AND ITS USE AGAINST CANCER

Background of the Invention

10 This invention relates to salt forms of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide having the formula I:



formula I.

Formula I in its free base form is described in co-pending United States Serial No. 09/883,752, filed June 18, 2001, the disclosure of which is hereby incorporated herein by reference in its entirety. The foregoing application is assigned in common with the present application. The free base of formula I is useful in the treatment of hyperproliferative diseases, such as cancers.

The present invention provides for succinate and malonate salt forms of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide.

The present invention also provides for the sesquisuccinate and di-malonate salt forms of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide.

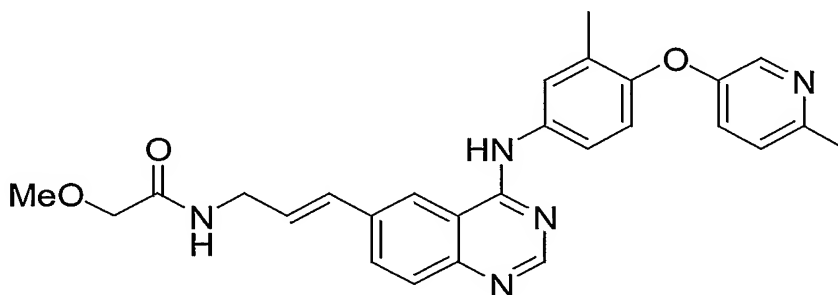
The present invention further relates to methods of making the sesquisuccinate and di-malonate salt forms of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide. The invention also relates to pharmaceutical compositions containing the sesquisuccinate and di-malonate salts of the compound of formula I. The salts of the present invention are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals, especially humans. The invention also relates to methods of administering the salts of formula I to treat hyperproliferative diseases.

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Summary of the Invention

The present invention relates to succinate and malonate salt forms of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide having the following formula I:



10

formula I.

In one preferred embodiment the invention relates to sesquisuccinate and di-malonate salt forms of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide

The present invention is also directed to processes for preparing the sesquisuccinate and di-malonate salts of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide comprising combining the free base with one of the aforementioned salts in the presence of a suitable organic solvent.

The sesquisuccinate and di-malonate salts of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide have been characterized by elemental analysis.

It has unexpectedly been found that the sesquisuccinate and di-malonate salts of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide have high crystallinity, i.e., substantially free of amorphous material. Such salts have the advantage that they provide more reproducible dosing results. The sesquisuccinate and di-malonate salts of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide are substantially hygroscopically stable, which alleviates potential problems associated with weight changes of the active ingredient during the manufacture of capsules or tablets.

The present invention also relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of succinate or malonate salt of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide, that is effective in treating abnormal cell growth. In one preferred embodiment, the invention relates to method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of sesquisuccinate or

5 di-malonate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)- phenylamino]-quinazolin-6-yl}-allyl)-acetamide, that is effective in treating abnormal cell growth.

In one embodiment the abnormal cell growth treated is cancer.

In one embodiment of the present the cancer is selected is selected from lung cancer, non small cell lung (NSCL) cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the
10 head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid
15 gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), colorectal cancer (CRC), primary CNS lymphoma, spinal axis tumors, brain stem glioma,
20 pituitary adenoma, or a combination of one or more of the foregoing cancers.

In a preferred embodiment of the present invention, cancer is selected from breast cancer, colon cancer, ovarian cancer, non small cell lung (NSCL) cancer, colorectal cancer (CRC), prostate cancer, bladder cancer, renal cancer, gastric cancer, endometrial cancer, head and neck cancer, and esophagel cancer.

25 In a more preferred embodiment of the present invention, the cancer is selected from renal cell carcinoma, gastric cancer, colon cancer, breast cancer, and ovarian cancer.

In a more preferred embodiment, the said cancer is selected from colon cancer, breast cancer or ovarian cancer.

Another embodiment of the present invention relates to method for the treatment of
30 abnormal cell growth in a mammal which comprises administering to said mammal an amount of succinate or malonate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide, that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell
35 cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

Another embodiment of the present invention relates to method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of sesquisuccinate or di-malonate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)- phenylamino]-quinazolin-6-yl}-allyl)-acetamide, that is effective in treating abnormal cell
40 growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors,

5 radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

Another embodiment of the present invention relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of succinate or malonate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-
10 phenylamino]-quinazolin-6-yl}-allyl)-acetamide, that is effective in treating abnormal cell growth in combination in combination with a cytotoxic.

In one preferred embodiment of the present invention the cytotoxic is Taxol® (paclitaxel).

The present invention further relates to a method for the treatment of abnormal cell
15 growth in a mammal which comprises administering to said mammal an amount of a succinate or malonate salt of formula 1 that is effective in treating abnormal cell growth in combination with a compound selected from the group consisting of Cyclophosphamide, 5-Fluorouracil, Floxuridine, Gemcitabine, Vinblastine, Vincristine, Daunorubicin, Doxorubicin, Epirubicin, Tamoxifen, Methylprednisolone, Cisplatin, Carboplatin, CPT- 11, gemcitabine, paclitaxel, and
20 docetaxel.

In one preferred embodiment, the invention relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a succinate or malonate salt of formula 1 that is effective in treating abnormal cell growth in combination with a compound selected from the group consisting Tamoxifen, Cisplatin,
25 Carboplatin, paclitaxel and docetaxel.

A preferred embodiment invention relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of sesquisuccinate or di-malonate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)- phenylamino]-quinazolin-6-yl}-allyl)-acetamide, that is effective in treating abnormal cell
30 growth in combination in combination with a cytotoxic.

In one preferred embodiment of the present invention the cytotoxic is Taxol® (paclitaxel).

The present invention further relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a
35 sesquisuccinate or di-malonate salt of formula 1 that is effective in treating abnormal cell growth in combination with a compound selected from the group consisting of Cyclophosphamide, 5-Fluorouracil, Floxuridine, Gemcitabine, Vinblastine, Vincristine, Daunorubicin, Doxorubicin, Epirubicin, Tamoxifen, Methylprednisolone, Cisplatin, Carboplatin, CPT- 11, gemcitabine, paclitaxel, and docetaxel.

40 In one preferred embodiment, the invention relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a sesquisuccinate or di-malonate salt of formula 1 that is effective in treating abnormal cell

5 growth in combination with a compound selected from the group consisting Tamoxifen, Cisplatin, Carboplatin, paclitaxel and docetaxel.

The invention further relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal comprising an amount of a succinate or malonate salt of formula 1, that is effective in treating abnormal cell growth, and a pharmaceutically acceptable
10 carrier.

The invention further relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal comprising an amount of a sesquisuccinate or di-malonate salt of formula 1, that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier.

15 This invention also relates to a method for the treatment of abnormal cell growth in a mammal, including a human, comprising administering to said mammal an amount of a sesquisuccinate or di-malonate salt of formula 1, or a solvate or prodrug thereof, that is effective in treating abnormal cell growth. In one embodiment of this method, the abnormal cell growth is cancer, including, but not limited to, lung cancer, non small cell lung (NSCL) cancer,
20 bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small
25 intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), colorectal cancer (CRC), primary CNS
30 lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In another embodiment of said method, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

This invention also relates to a method for the treatment of abnormal cell growth in a
35 mammal, including a human, which comprises administering to said mammal a sesquisuccinate or di-malonate salt of formula 1, or a solvate or prodrug thereof, that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers,
40 antibodies, cytotoxics, anti-hormones, and anti-androgens.

This invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, comprising an amount of a

5 sesquisuccinate or di-malonate salt of formula 1, or a solvate or prodrug thereof, that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier. In one embodiment of said composition, said abnormal cell growth is cancer, including, but not limited to, lung cancer, non small cell lung (NSCL) cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer,
10 rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft
15 tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), colorectal cancer (CRC), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers. In another
20 embodiment of said pharmaceutical composition, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

The invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, which comprises a succinate or
25 malonate salt of formula 1 or a solvate or prodrug thereof, that is effective in treating abnormal cell growth in combination with a pharmaceutically acceptable carrier and an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

30 The invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, which comprises a sesquisuccinate or di-malonate salt of formula 1 or a solvate or prodrug thereof, that is effective in treating abnormal cell growth in combination with a pharmaceutically acceptable carrier and an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-
35 metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

The invention also relates to a method for treating a mammal having cancer characterized by an overexpression of erbB2, comprising administering to the mammal a succinate or malonate salt of formula 1 in an amount that is effective in treating said cancer
40 characterized by the overexpression of erbB2.

A preferred embodiment of the present invention relates to a method for treating a mammal having cancer characterized by an overexpression of erbB2, comprising

5 administering to the mammal a sesquisuccinate or di-malonate salt of formula 1 in an amount that is effective in treating said cancer characterized by the overexpression of erbB2.

The invention also relates to a method for treating a mammal having a disease characterized by an overexpression of erbB2, comprising administering to the mammal a succinate or malonate salt of formula 1 in an amount that is effective in treating a disease
10 characterized by the overexpression of erbB2.

A preferred embodiment of the present invention relates to a method for treating a mammal having a disease characterized by an overexpression of erbB2, comprising administering to the mammal a sesquisuccinate or di-malonate salt of formula 1 in an amount that is effective in treating a disease characterized by the overexpression of erbB2.

15 The invention also relates to a method inducing cell death comprising exposing a cell which overexpresses erbB2 to an effective amount of a succinate or malonate salt of formula 1. In one embodiment the cell is a cancer cell in a mammal, preferably a human.

A preferred embodiment of the present invention relates to a method of inducing cell death comprising exposing a cell which overexpresses erbB2 to an effective amount of a sesquisuccinate or di-malonate salt of formula 1. In one embodiment the cell is a cancer cell
20 in a mammal, preferably a human.

The present invention relates to a method inducing cell death comprising exposing a cell which overexpresses erbB2 to an effective amount of a succinate or malonate salt of formula 1 and said method further comprises exposing the cell to a growth inhibitory agent.

25 In another embodiment the present invention relates to a method inducing cell death comprising exposing a cell which overexpresses erbB2 to an effective amount of a sesquisuccinate or di-malonate salt of formula 1 and said method further comprises exposing the cell to a growth inhibitory agent.

In one preferred embodiment the cell is exposed to a chemotherapeutic agent or
30 radiation.

The invention further relates to a method of treating cancer in a human, wherein the cancer expresses the erbB2 receptor, comprising administering to the human a therapeutically effective amount of a succinate or malonate salt of formula 1. In a preferred embodiment the invention relates to a method of treating cancer in a human, wherein the cancer expresses the
35 erbB2 receptor, comprising administering to the human a therapeutically effective amount of a sesquisuccinate or di-malonate salt of formula 1. In one preferred embodiment of the present invention the cancer is not characterized by overexpression of erbB1 receptor. In another preferred embodiment the cancer is characterized by overexpression of the erbB1 and erbB2 receptor.

40 This invention also relates to a method for the treatment of a disorder associated with angiogenesis in a mammal, including a human, comprising administering to said mammal a succinate or malonate salt of formula 1, or solvate or prodrug thereof, that is effective in

5 treating said disorder. In a preferred embodiment the invention relates a method for the treatment of a disorder associated with angiogenesis in a mammal, including a human, comprising administering to said mammal a sesquisuccinate or di-malonate salt of formula 1, or solvate or prodrug thereof, that is effective in treating said disorder. Such disorders include cancerous tumors such as melanoma; ocular disorders such as age-related macular
10 degeneration, presumed ocular histoplasmosis syndrome, and retinal neovascularization from proliferative diabetic retinopathy; rheumatoid arthritis; bone loss disorders such as osteoporosis, Paget's disease, humoral hypercalcemia of malignancy, hypercalcemia from tumors metastatic to bone, and osteoporosis induced by glucocorticoid treatment; coronary restenosis; and certain microbial infections including those associated with microbial
15 pathogens selected from adenovirus, hantaviruses, *Borrelia burgdorferi*, *Yersinia spp.*, *Bordetella pertussis*, and group A *Streptococcus*.

"Abnormal cell growth", as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras
20 oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs; and (4) any tumors that proliferate by virtue of farnesyl protein transferase.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term
25 applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

The term "a compound that has reduced affinity for the erbB1 receptor", as used herein, unless otherwise indicated, means wherein the compound is an erbB2 inhibitor and has a
30 range of selectivities for erbB2 receptor over the erbB1 receptor between 50-1500, i.e., the compound is from 50 to 1500 times more selective for the erbB2 receptor over the erbB1 receptor. In a preferred embodiment the erbB2 inhibitor has a range of selectivities for erbB2 over erbB1 between 60-1200. In a more preferred embodiment the erbB2 inhibitor has a range of selectivities for erbB2 over erbB1 between 80-1000. In an even more preferred
35 embodiment the erbB2 inhibitor has a range of selectivities for erbB2 over erbB1 between 90-500. In a most preferred embodiment the erbB2 inhibitor has a range of selectivities for erbB2 over erbB1 between 100-300. In the most preferred embodiment the erbB2 inhibitor has a range of selectivities for erbB2 over erbB1 between 110-200. The selectivity of the erbB2 inhibitor over the erbB1 inhibitor is measured using the whole cell (intact) assay described
40 below.

Detailed Description of the Invention

5 The present invention relates to succinate and malonate salts of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide.

 In one preferred embodiment of the present invention relates to sesquisuccinate and di-malonate salts of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide.

10 The invention further relates to a method making the sesquisuccinate and di-malonate salts of E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide. The salt forms of the present invention are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

15 The salt forms of the compound of formula I have been characterized using elemental analysis.

 The *in vitro* activity of the compounds of formula 1 may be determined by the following procedure.

 The *in vitro* activity of the compounds of formula 1 as erbB kinase inhibitors in intact
20 cells may be determined by the following procedure. Cells, for example 3T3 cells transfected with human EGFR (Cohen et al. J. Virology 67:5303, 1993) or with chimeric EGFR/erbB2 kinase (EGFR extracellular/erbB2 intracellular, Fazioli et al. Mol. Cell. Biol. 11: 2040, 1991) are plated in 96-well plates at 12,000 cells per well in 100 μ l medium (Dulbecco's Minimum Essential Medium (DMEM) with 5% fetal calf serum, 1% pen/streptomycin, 1% L-glutamine)
25 and incubated at 37° C, 5% CO₂. Test compounds are solubilized in DMSO at a concentration of 10 mM, and tested at final concentrations of 0, 0.3 μ M, 1 μ M, 0.3 μ M, 0.1 μ M and 10 μ M in the medium. The cells are incubated at 37° C for 2 h. EGF (40 ng/ml final) is added to each well and cells incubate at room temperature for 15 min followed by aspiration of medium, then 100 μ l/well cold fixative (50% ethanol/50% acetone containing 200 micromolar sodium
30 orthovanadate) is added. The plate is incubated for 30 min at room temperature followed by washing with wash buffer (0.5% Tween 20 in phosphate buffered saline). Blocking buffer (3% bovine serum albumin, 0.05% Tween 20, 200 μ M sodium orthovanadate in phosphate buffered saline, 100 μ l/well) is added followed by incubation for 2 hours at room temperature followed by two washes with wash buffer. PY54 monoclonal anti-phosphotyrosine antibody
35 directly conjugated to horseradish peroxidase (50 μ l/well, 1 μ g/ml in blocking buffer) or blocked conjugate (1 μ g/ml with 1 mM phosphotyrosine in blocking buffer, to check specificity) is added and the plates incubated for 2 hours at room temperature. The plate wells are then washed 4 times with wash buffer. The colorimetric signal is developed by addition of TMB Microwell Peroxidase Substrate (Kirkegaard and Perry, Gaithersburg, MD), 50 μ l per well, and
40 stopped by the addition of 0.09 M sulfuric acid, 50 μ l per well. Absorbance at 450 nm represents phosphotyrosine content of proteins. The increase in signal in EGF-treated cells

5 over control (non-EGF treated) represents the activity of the EGFR or EGFR/chimera respectively. The potency of an inhibitor is determined by measurement of the concentration of compound needed to inhibit the increase in phosphotyrosine by 50% (IC₅₀) in each cell line. The selectivity of the compounds for erbB2 vs. EGFR is determined by comparison of the IC₅₀ for the EGFR transfectant vs. that for the erbB2/EGFR chimera transfectant. Thus, for
10 for example, a compound with an IC₅₀ of 100 nM for the EGFR transfectant and 10 nM for the erbB2/EGFR chimera transfectant is considered 10-fold selective for erbB2 kinase.

Administration of the compounds of the present invention (hereinafter the "active compound(s)") can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection
15 (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration.

The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration and the judgement of the prescribing physician. However, an effective dosage is in the range of about
20 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to about 7 g/day, preferably about 0.2 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first
25 divided into several small doses for administration throughout the day.

The active compound may be applied as a sole therapy or may involve one or more other anti-tumour substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, cytosine arabinoside and
30 hydroxyurea, or, for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example interferon; and anti-hormones, for example anti-estrogens such as NolvadexTM (tamoxifen) or, for example
35 anti-androgens such as CasodexTM (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide). Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution,
40 suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The

5 pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

10 Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, 15 tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. 20 Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

25 Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

The examples and preparations provided below further illustrate and exemplify the 30 compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. 35 Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

Where HPLC chromatography is referred to in the preparations and examples below, the general conditions used, unless otherwise indicated, are as follows. The column used is a ZORBAX™ RXC18 column (manufactured by Hewlett Packard) of 150 mm distance and 4.6 40 mm interior diameter. The samples are run on a Hewlett Packard-1100 system. A gradient solvent method is used running 100 percent ammonium acetate / acetic acid buffer (0.2 M) to

5 100 percent acetonitrile over 10 minutes. The system then proceeds on a wash cycle with 100 percent acetonitrile for 1.5 minutes and then 100 percent buffer solution for 3 minutes. The flow rate over this period is a constant 3 mL/ minute.

In the following examples and preparations, "Et" means ethyl, "AC" means acetyl, "Me" means methyl, "ETOAC" or "ETOAc" means ethyl acetate, "THF" means tetrahydrofuran, and "Bu" means butyl.

Example 1

Free base of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide

15

The free base of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide is prepared according Example 182 (LMRS: 470.1, HPLC RT:5.05) using procedure G described in United States Serial No. 09/883,752, filed June 18, 2001, the disclosure of which is hereby incorporated herein by reference in its entirety. Procedure G from United States Serial No. 09/883,752, is shown below:

20

Method G: Synthesis of *E*-N-(3-{4-[3-Chloro-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide (7):

E-(3-{4-[3-chloro-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-carbamic acid *tert*-butyl ester: To a solution of 7.53 mL of a 65% weight toluene solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, 24.2 mmol) in 90 mL of tetrahydrofuran at 0°C was added 5.0 g of (3-{4-[3-chloro-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-carbamic acid *tert*-butyl ester as a solid. The reaction was stirred at 0°C for 2 hours, quenched with 10% aqueous potassium carbonate and extracted with ethyl acetate. The combined organics were dried and evaporated. The crude material was purified on 115 g of silica gel, eluting with 80% ethyl acetate/ hexanes to afford 4.42 g of *E*-(3-{4-[3-chloro-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-carbamic acid *tert*-butyl ester. ¹H NMR (CDCl₃): δ 8.66 (s, 1), 8.24 (m, 1), 8.03 (m, 2), 7.77-7.65 (m, 3), 7.13 (m, 2), 6.97 (d, J = 8.7 Hz, 1), 6.54 (d, 1), 6.35 (m, 1), 4.9 (m, 1), 3.90 (m, 2), 2.52 (s, 3), 1.46 (s, 9).

35

E-[6-(3-amino-propenyl)-quinazolin-4-yl]-[3-chloro-4-(6-methyl-pyridin-3-yloxy)-phenyl]-amine. To a solution of 4.42 g of *E*-(3-{4-[3-chloro-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-carbamic acid *tert*-butyl ester in 21 mL of tetrahydrofuran was added 21 mL of 2 N hydrochloric acid. The mixture was heated at 60°C for 3 hours, cooled to room temperature and basified with 10% aqueous potassium carbonate. Methylene chloride was added to the aqueous mixture and a solid precipitated. The solid was filtered

40

5 and dried to yield 2.98 g of *E*-[6-(3-amino-propenyl)-quinazolin-4-yl]-[3-chloro-4-(6-methyl-pyridin-3-yloxy)-phenyl]-amine. ¹H NMR (d₆ DMSO): δ 8.62 (s, 1), 8.53 (m, 1), 8.26 (m, 2), 7.99 (m, 1), 7.89 (m, 1), 7.77 (m, 1), 7.30 (m, 3), 6.67 (m, 2), 3.44 (m, 2), 2.47 (s, 3).

***E*-N-(3-{4-[3-Chloro-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide.** A mixture of 14.4 μL (0.25 mmol) of acetic acid and 40.3 mg (0.33 mmol) of
10 dicyclohexylcarbodiimide in 2 mL of methylene chloride were stirred for 10 minutes and treated with 100.3 mg of *E*-[6-(3-amino-propenyl)-quinazolin-4-yl]-[3-chloro-4-(6-methyl-pyridin-3-yloxy)-phenyl]-amine. The reaction was allowed to stir at room temperature overnight. The precipitate which formed was filtered and chromatographed on silica gel, eluting with 6-10% methanol/chloroform to afford 106 mg of the title compound; mp 254-
15 256°C; ¹H NMR (d₆ DMSO): δ 9.88 (s, 1), 8.58 (s, 1), 8.48 (m, 1), 8.20 (m, 3), 7.95 (m, 1), 7.83 (m, 1), 7.71 (d, J = 8.7 Hz, 1), 7.24 (m, 2), 7.19 (d, J = 8.7 Hz, 1), 6.61 (d, J = 16.2 Hz, 1), 6.48 (m, 1), 3.90 (m, 2).

Example 2

Sesquisuccinate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide
20

To a solution of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide in hot THF/acetone (5/100) two equivalents of succinic acid were added. Crystals slowly formed as the solution cooled. After slurring
25 overnight, the crystals were filtered and rinsed with acetone. The product was isolated as a white solid and verified as the sesquisuccinate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide by CHN analysis. Calculated: C=61.29, H=5.61, N=10.83, Experimental: C=61.04, H=5.61, N=10.85.

30

Example 3

Di-malonate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide

To a solution of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide (1g) in hot acetone (100ml) was added two
35 equivalents of malonic acid (443mg). As the solution cooled crystals formed after 2 hours, the crystals were filtered after slurring overnight and rinsed with acetone. The light yellow solid (1.36g, 94%) was confirmed as the di-malonate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide by CHN analysis.
40 Calculated: C=58.49, H=5.21, N=10.33, Experimental: C=58.30, H=5.12, N=10.33

5

CLAIMS

What is claimed is:

1. A succinate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)- phenylamino]-quinazolin-6-yl}-allyl)-acetamide.
- 10 2. The compound of claim 1, wherein the succinate salt is a sesquisuccinate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)- phenylamino]-quinazolin-6-yl}-allyl)-acetamide.
- 15 3. A method of treating abnormal cell growth in a mammal comprising administering to said mammal an amount of a sesquisuccinate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide that is effective in treating abnormal cell growth.
- 20 4. A method according to claim 3, wherein said abnormal cell growth is cancer.
- 25 5. The method according to claim 4 wherein said cancer is selected from lung cancer, non small cell lung (NSCL) cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), colorectal cancer (CRC), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers.
- 30 6. A method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound of claim 1 that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.
- 40

5 7. The method of claim 6, which comprises administering to said mammal an amount of a compound of claim 1 that is effective in treating abnormal cell growth in combination with a cytotoxic.

8. A method for the treatment of abnormal cell growth in a mammal which
10 comprises administering to said mammal an amount of the compound of claim 1 that is effective in treating abnormal cell growth in combination with a compound selected from the group consisting of Cyclophosphamide, 5-Fluorouracil, Floxuridine, Gemcitabine, Vinblastine, Vincristine, Daunorubicin, Doxorubicin, Epirubicin, Tamoxifen, Methylprednisolone, Cisplatin, Carboplatin, CPT- 11, gemcitabine, paclitaxel, and docetaxel.

15

9. A pharmaceutical composition comprising an amount of a compound according to claim 1 effective to treat a hyperproliferative disorder in a mammal, and a pharmaceutically acceptable carrier.

20

10. A malonate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide.

25

11. The compound of claim 10, wherein the malonate salt is a di-malonate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide.

30

12. A method of treating abnormal cell growth in a mammal comprising administering to said mammal an amount of a di-malonate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide that is effective in treating abnormal cell growth.

35

13. A method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound of claim 12 that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

40

14. A process for preparing a succinate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide comprising reacting *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide and succinic acid .

5

15. A process for preparing a malonate salt of *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide comprising reacting *E*-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide (1g) and malonic acid .

10

INTERNATIONAL SEARCH REPORT

PCT/IB 02/04708

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 98277 A (KATH JOHN CHARLES ;MORRIS JOEL (US); PFIZER PROD INC (US); BHATTAC) 27 December 2001 (2001-12-27) page 1, line 1-12 claim 1	1-15
X	WO 96 09294 A (WELLCOME FOUND ;HUDSON ALAN THOMAS (GB); VILE SADIE (GB); BARRACLO) 28 March 1996 (1996-03-28) page 1, paragraphs 1,2; claim 1	1-15
A	WO 98 02434 A (COCKERILL GEORGE STUART ;GUNTRIP STEPHEN BARRY (GB); GLAXO GROUP L) 22 January 1998 (1998-01-22) page 1, line 1-17; claim 1	1-15
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 January 2003

Date of mailing of the international search report

15/01/2003

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INTERNATIONAL SEARCH REPORT

PCT/IB 02/04708

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 97 30034 A (ZENECA LTD) 21 August 1997 (1997-08-21) page 1, line 1-8 claim 1</p> <p>-----</p>	1-15

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 3-8,12 and 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

PCT/IB 02/04708

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

patent family members

PCT/IB 02/04708

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